REMARKS

Claims 1, 3-9, 11-17, and 19-34 will be pending in the application, after entry of the amendments. Claims 19-32 have been withdrawn from consideration. No claim stands allowed.

Claim 18 has been canceled without prejudice or disclaimer. Claims 1, 6-9, 13-17, 33 and 34 have been amended to replace the term "esomeprazole" with "(S)-5-methoxy-2-[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole." Support for this amendment can be found throughout the specification and claims as originally filed, *e.g.*, page 1, lines 8-16. Claim 33 has also been amended to specify that the pharmaceutical composition is solid, and claim 34 has also been amended to indicate that the subject is administered a solid pharmaceutical composition comprising esomeprazole. Support for these amendments can be found throughout the specification and claims as originally filed, *e.g.*, page 12, line 18 to page 14, line 12. No new matter has been introduced by these amendments.

Reconsideration of the claim rejections and allowance of the pending claims in view of the amendments above and following remarks are respectfully requested.

Claim Rejections – 35 U.S.C. § 102

Claims 1, 3-9, 11-17, 33 and 34 were rejected under 35 U.S.C. §§ 102(a) and/or (e) as allegedly anticipated by Cotton et al (U.S. Patent No. 6,369,085; "Cotton"). According to the Examiner, Cotton specifically discloses the instant compound. Particular attention is directed to Example 1 and column 2, lines 47-50, which states that "[t]he compound of the invention is characterized by being highly crystalline, i.e. having a higher crystallinity than any other form of magnesium salt of S-omeprazole disclosed in the prior art." The Examiner states that the Applicants have failed to present any X-ray diffraction for the instant compound and composition vis-à-vis the prior art compound. Applicants respectfully traverse this basis for rejection.

It has long been the law that anticipation can properly be held only where a prior art document teaches each and every limitation of the rejected claim. *See Verdegaal Bros. v. Union Oil Co. of Cal.*, 814 F.2d 628, 631 (Fed. Cir. 1987). Here, each of the rejected claims is directed to a crystalline form II of esomeprazole magnesium trihydrate

having substantially the same X-ray diffraction pattern as shown in Fig. 1 of the instant specification.

Contrary to the Examiner's position, Applicants have provided X-ray diffraction data that clearly demonstrates that the esomeprazole magnesium trihydrate of Cotton has an X-ray diffraction pattern distinctly different from that of the instantly claimed compound. As noted by the Applicants in their Appeal Brief submitted on September 5, 2006 ("Appeal Brief"), even a cursory inspection reveals that the X-ray diffraction pattern for the instant crystalline form II of esomeprazole magnesium trihydrate shows, *inter alia*, very prominent peaks at about 4.8 and 18.5 degrees two-theta that are completely absent from the pattern for the esomeprazole magnesium trihydrate disclosed in Cotton, while the X-ray diffraction pattern for the esomeprazole magnesium trihydrate of Cotton shows, *inter alia*, a very prominent peak at about 22.5 degrees two-theta that is completely absent from the pattern for the instant crystalline form II of esomeprazole magnesium trihydrate. (*Compare* Fig. 1 and the table at page 6 of the instant specification with Fig. 1 of Cotton.)

Applicants submit that incorporation of the X-ray diffraction pattern of Fig. 1 into the instant claims adequately distinguishes the claimed subject matter from that of Cotton. Accordingly, Applicants submit that claims 1, 3-9, 11-17, 33 and 34 are not anticipated, and reconsideration of this basis for rejection is respectfully requested.

Claim Rejections – 35 U.S.C. § 103

Claims 1, 3-9, 11-17, 33 and 34 were rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Cotton in view of Bohlin et al. (U.S. Pat. No. 6,162,816; "Bohlin"), Lindberg et al. (U.S. Pat. No. 6,875,872; "Lindberg"), Haleblian et al. (*J. Pharm. Sciences*, (1969), 58 pp. 911-929; "Haleblian"), Muzaffar et al. (*J. of Pharmacy* (Lahore) 1979, 1(1), 59-66; "Muzaffer"), Chemical & Engineering News, Feb. 2003 ("C&E News"), U.S. Pharmacopia, 1995, pp. 1843-1844 ("USP") and Concise Encyclopedia Chemistry, pages 872-873 (1993) ("CEC"). According to the Examiner, Cotton teaches the crystalline form of the magnesium salt of esomperazole. Bohlin and Lindberg are said to teach that esomeprazole and its salts can exist in different crystalline states. Muzaffar and Haleblian are said to teach that compounds can exist in

amorphous forms as well as crystalline states. C&E News, USP and CEC are said to teach that at any particular temperature and pressure, only one crystalline form is thermodynamically stable. Thus, according to the Examiner, it would appear to one skilled in the art in view of the references that the instant compound would exist in different crystalline forms. No unexpected or unobvious properties were noted by the Examiner. Applicants respectfully traverse this basis for rejection.

The standards for making an obviousness rejection are summarized in MPEP § 706.02(j) as follows:

> To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art and not based on applicant's disclosure. *In re Vaeck,* 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

As discussed above, Cotton discloses a crystalline form of esomeprazole magnesium trihydrate, but does not teach or suggest crystalline form II of esomeprazole magnesium trihydrate having substantially the same X-ray diffraction pattern as shown in Fig. 1 of the instant specification. Similarly, Bohlin discloses that esomeprazole base can exist in amorphous, partly crystalline or substantially crystalline solid states, while Lindberg discloses crystalline esomeprazole magnesium, but neither teach nor suggest crystalline form II of esomeprazole magnesium trihydrate having substantially the same X-ray diffraction pattern as shown in Fig. 1 of the instant specification. The ancillary references cited by the Examiner merely provide general background information relating to the study and preparation of polymorphs or case histories of specific polymorphic compounds (none of which is esomeprazole magnesium trihydrate), and thus add nothing over the primary references. As such, none of the cited references, alone or in combination teach or suggest the instantly claimed compound with all its limitations. This alone is enough to overcome the Examiner's obviousness rejection.

See Ex parte Havens, Appeal No. 2001-0091 for U.S. Pat. Appl. No. 08/732,254, now U.S. Pat. No. 6,452,007 (BPAI 2001) ("The examiner's obviousness rejection seems to suffer the same infirmity as her anticipation rejection . . . The examiner has provided no evidence or convincing reason why the prior art disclosure of delavirdine mesylate in an undefined state would have suggested the specific S and T crystal forms that are the subject of the instant claims.") (emphasis added).

As noted by the Applicants in their Appeal Brief, the proper test for obviousness in this case is not whether the existence of esomeprazole magnesium trihydrate polymorphs is suggested by the prior art, but whether it would have been obvious to make the particular esomeprazole magnesium trihydrate claimed in the instant application based on the prior art:

> The law of § 103 requires quite a different inquiry from that conducted by the ALJ. Thee correct inquiry is not whether the Bouzard monohydrate [polymorph] could have been produced by manipulation of other cefadroxil processes, once the existence of the Bouzard monohydrate was known. The question is whether it would have been obvious to make the Bouzard monohydrate, based on the prior art.

Bristol-Myers Co. v. U.S. Int'l Trade Comm'n, 892 F.2d 1050, (Fed. Cir. Dec. 8, 1989) (unpublished decision) (emphasis added).

Here, the references cited by the Examiner suggest at most the possibility of other esomeprazole magnesium trihydrate polymorphs. The Examiner has pointed to nothing in the cited references, however, that would suggest to one skilled in the art the particular form claimed in the instant application, or a method for its preparation. In fact, CEC, p. 32, cited by the Examiner, states that "no method yet exists to predict the polymorphs of a solid compound with significant certainty." The Examiner admits as much by quoting the passage under the enablement rejection at page 10 of the Office Action (discussed *infra*).

As was done in the previous Office Action mailed on April 6, 2006, the Examiner again contends that:

> [A]s set forth by the court in In re Cofer 148 USPQ 268, Ex parte Hartop 139 USPQ 5252, that a product which are merely different forms of known compounds, notwithstanding that some desirable results are obtained thereform, are

> unpatentable. The instant claims are drawn to the ***same pure substance*** as the prior art that only having *different arrangements and or different conformations of the molecule*. A mere difference in physical property is a well known conventional variation for the same pure substance is prima facie obvious. (Emphasis in original.)

The Examiner still appears to be taking the position that new polymorphs are *per se* unpatentable over the originally identified compound or previously identified polymorphs of the same compound. Such a rule, however, is inconsistent with the law on obviousness. *See Ex parte Andrews*, Appeal No. 2002-0941 for U.S. Pat. Appl. No. 09/166,445, now U.S. Pat. No. 6,713,481 (BPAI 2003) (quoting *In re Ochiai*, 71 F.3d 1565 (Fed. Cir. 1995) ("The use of *per se* rules flouts § 103 and the fundamental case law applying it. . . [R]eliance on *per se* rules of obviousness is legally incorrect and must cease.").

Applicants maintain that the Examiner's reliance on *In re Cofer* and *Ex parte Hartop* is misplaced in this case. *In re Cofer* actually held the claimed crystalline 2,2-bis patentable because

> [T]he board failed to address . . . whether the prior art suggests the particular structure or form of the compound or composition as well as suitable methods of obtaining the structure or form. (Emphasis added.)

354 F.2d 664, 668 (CCPA 1966).

The *Cofer* court addressed the *Ex parte Hartop* decision, which had been relied upon by the board in finding the claimed crystalline 2,2-bis unpatentable:

> We think examination of the decisions relied on . . . in *Hartop* will demonstrate that the materials involved therein were found unpatentable where the alleged difference in form or purity of those substances was either disclosed or inherent therein. (Emphasis added.)

Id. at 667.

Here, as discussed above, the references cited by the Examiner neither disclose or suggest the particular esopmeprazole magnesium trihydrate disclosed and claimed in the instant application.

As the Applicants noted in their Appeal Brief, the Board of Patent *Appeals* & Interferences has recently cautioned against the reliance on *Ex parte Hartop* in polymorph cases. As stated in *Ex parte Gala*:

> The examiner relies heavily on this proposition of law set forth in *Ex parte Hartop* . . . : "[m]erely changing the form, purity or another characteristic of an old product, the utility remaining the same as that for the old product, does not render the claimed product patentable." According to the examiner, polymorph form 2 loratadine is merely another form of an old product (polymorph form 1 loratadine) and both forms possess the same utility. Accordingly, the examiner concludes that applicants' claims, reciting polymorph form 2 loratadine, are unpatentable. We disagree. Here, we invite attention to *In re Cofer* . . . , where the court substantially discredited PTO reliance on the above-quoted proposition of law in *Hartop*. Like the situation presented in *Cofer*, the examiner in this case has not adequately established that the prior art (1) suggests the polymorph form 2 of loratadine; or (2) discloses or renders obvious a method for making the polymorph form 2 of loratadine. (Emphasis added.)

Appeal No. 2001-0987 for U.S. Pat. Appl. No. 0/169,109, now U.S. Pat. No. 6,335,347 (BPAI 2001); *see also Ex parte Andrews*, *supra* ("[T]he principal of law enunciated in *Ex parte Hartop* . . . has been substantially discredited in *In re Cofer* . . .").

According to the Examiner, Applicants do not point to any objective evidence which demonstrates that the claimed compound exhibits any properties which are actually different from the closest prior compounds. The Examiner also states that Applicants' assertion in their Appeal Brief that the USPTO routinely issues patents to new solid state forms is not persuasive. The Examiner points to page 185 of Brittain ("Polymorphism in Pharmaceutical Solids," 1999, pp. 183-226), which states that "[i]n 1990 Byrn and Pfeiffer found that more than 350 patents on crystal forms granted on the basis of an advantage in terms of stability, formulation, solubility, bioavailability, ease of purification, etc."

First, Applicants note that the cited Brittain passage supports their assertion that the USPTO routinely issues patents directed to new polymorphs, thus evidencing that they are patentable subject matter. In addition, the endnote for the passage states that

its content was personally communicated to Brittain by Bryn in 1996. There is no discussion in Brittain of the subject matter of the patents, the prior art of record (if any), the bases for rejections (if any) or the effect of the purported advantages on allowance (if any).

In any event, Applicants respectfully submit that unexpected properties need not be demonstrated in this case because a *prima facie* case of obviousness has not been made under the proper test described above. The CCPA in *In re Grose* specifically rejected the application of the law of structural obviousness, and hence a requirement for a showing of unexpected properties, when analyzing the patentability of new solid state forms:

> No reason exists for applying the law relating to structural obviousness of those compounds which are homologs or isomers of each other to this case. . . . A zeolite, like those of the instant case, is not a compound which is a homolog or isomer of another, but is a mixture of various compounds related to each other by a particular crystal structure. Moreover, no other chemical theory has been cited as a basis for considering appellants' zeolite as prima facie obvious in view of [the prior art] zeolite R.

592 F.2d 1161, 1167-68 (CCPA 1979).

Accordingly, Applicants submit claims 1, 3-9, 11-17, 33 and 34 are not unpatentable over Cotton in view of Bohlin, Lindberg, Haleblian, Muzaffar, C&E News, USP and CEC, and reconsideration of this basis for rejection is respectfully requested.

Claim Rejections – 35 U.S.C. § 112

(a) Claims 33 and 34 were rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description and enablement requirements. According to the Examiner, there is a lack of description as to whether the compositions are able to maintain the compound in the crystalline form claimed. Similarly, according to the Examiner, the specification lacks direction or guidance for maintaining the compound in the crystalline form claimed. In particular, the Examiner states that metastable crystalline forms disappear and change into the most thermodynamically

stable form, and all crystalline forms become amorphous in solution. Applicants respectfully traverse this basis for rejection.

Claims 33 and 34 are directed to a solid pharmaceutical composition comprising crystalline form II of esomeprazole magnesium trihydrate having substantially the same X-ray diffraction pattern as shown in Fig. 1 of the instant specification, and a method for reducing gastric acid secretion in a subject comprising administration of such a solid pharmaceutical composition. As noted in Applicants' Appeal Brief, the claims contain no limitation requiring that the crystalline form be maintained indefinitely, or that it be the only form present, and Applicants submit that it is error to read such a limitation into the claims. Applicants maintain that the instant specification clearly describes and enables the preparation of compositions comprising crystalline form II esomeprazole magnesium trihydrate having substantially the same X-ray diffraction pattern as shown in Fig. 1 of the instant specification, and methods of treatment comprising the same. *See, e.g.*, page 11, line 26 to page 15, line 12. Furthermore, the specification clearly describes and enables methods for identifying and monitoring the presence of crystalline form II esomeprazole magnesium trihydrate in the claimed composition before, during and after its preparation. *See, e.g.*, page 5, line 32 to page 9, line 22.

In addition, Applicants submit that reading claims 33 and 34 to encompass compounds and compositions where all crystalline form II esomeprazole magnesium trihydrate is lost (and hence its solid state characteristics are also lost) is contrary to the plain meaning of the claim language. Claims 33 and 34 specifically recite "crystalline Form II of esomeprazole magnesium trihydrate, having substantially the same X-ray diffraction pattern as shown in Figure 1," meaning that esomeprazole magnesium trihydrate in solution (and thus lacking any crystalline structure with the specifically recited XRD pattern) is outside the scope of these claims. However, in the interest of expediting prosecution, claims 33 and 34 have been amended to specify that the composition is solid.

With regard to the Examiner's contention that metastable crystalline forms disappear and change into the most thermodynamically stable form, Applicants note that several of the references cited by the Examiner explain that such transformation

can be very slow (on the order of years) owing to the relative stability of the metastable form. As Muzaffar notes at page 60:

> When the rate of conversion of a metastable form is so slow as to be negligible, the solubility of the compound will be maximal and will have a faster rate of dissolution and hence absorption. This biopharmaceutical property of the polymorphs could be explained for achieving better results in the formulation of drugs, especially in the unit dosage forms of the drugs.

Thus, even assuming that crystalline form II esomeprazole magnesium trihydrate is a metastable form (mere conjecture at this point), its possible transformation at some point in the future does not detract from its utility while in the claimed form. Again, any esomeprazole magnesium trihydrate not having substantially the same X-ray diffraction pattern as shown in Figure 1 is outside the scope of the claims.

Accordingly, Appellants submit that claims 33 and 34 are adequately described and enabled, and reconsideration of this basis for rejection is respectfully requested.

(b) Claims 1, 6-9, 13-17, 33 and 34 were rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite. According to the Examiner, the rejected claims recite the chemical name "esomeprazole," which the Examiner believes is a trade name. Citing *Ex parte Simpson*, 218 USPQ 1020 (BPAI 1982), the Examiner states that the use of a trade name renders the claim scope uncertain since it cannot be used properly to identify a particular material or product. The Examiner believes only the IUPAC name for esomeprazole will render the rejected claims definite.

As noted by Applicants in their Appeal Brief, "esomeprazole" is not a trademark or trade name, but rather the name assigned by the U.S. Adopted Names ("USAN") Council, a cooperative effort among the American Medical Association ("AMA"), the U.S. Pharmacopeial ("USP") Convention and the American Pharmacists Association ("APA"). Esomeprazole magnesium is shown in the electronic version of the U.S. FDA's Orange Book as the active ingredient in AstraZeneca's product having the proprietary name "Nexium®". Thus, esomeprazole magnesium is a generic name which identifies its structure, and Nexium® is a trade name which identifies its commercial source.

Again, the Examiner provides no support for the proposition that only an IUPAC name will suffice to render a claim definite.

However, solely in the interest of expediting prosecution, Applicants have amended claims 1, 6-9, 13-17, 33 and 34 to replace the term "esomeprazole" with the IUPAC name "(S)-5-methoxy-2-[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole," thereby rending the rejection moot.

(c) Claim 18 was rejected under 35 U.S.C. § 112, second paragraph, as allegedly being drawn to the same scope as claim 1. According to the Examiner, citing *In re Hughes*, 182 USPQ 106 (CCPA 1974), product-by process claims are not proper in the same application where it is demonstrated that the compound in question may be described by means of a chemical structure.

As noted by Applicants in their Appeal Brief, there is no statutory or regulatory prohibition against the use of both product and product-by-process claims in the same application. Indeed, the MPEP specifically sanctions the unrestricted use of such claims. *See* MPEP § 2173.05(p) ("A product-by-process claim, which is a product claim that defines the claimed product in terms of the process by which it is made, is proper.") (citations omitted). This has been recognized by the Federal Circuit in *Smithkline Beecham Corp. v. Apotex Corp.*, where the court stated that "product-by process claims are used by inventors even if the invention could have been described independent of the process." 493 F.3d 1312, 1315 and n.2 (Fed. Cir. 2006) (citing 3 Chisum on Patents § 8.05[2][c] (2003 ed.) (explaining that the USPTO has rejected the "necessity rule" for product-by-process claims, allowing them so long as they meet the definiteness requirement).

However, solely in the interest of expediting prosecution, Applicants have cancelled claim 18, thereby rending the rejection moot.

CONCLUSION

It is believed that claims 1, 3-9, 11-17, 33 and 34 are in condition for allowance, early notice of which would be appreciated. If any minor matters remain to be resolved,

please contact the undersigned to arrange for a telephonic or personal interview to expedite resolution.

Respectfully submitted,

/R. A. Franks/

Robert A. Franks
Attorney for Applicants
Reg. No. 28,605

February 21, 2007

Dr. Reddy's Laboratories, Inc.
200 Somerset Corporate Blvd., Seventh Floor
Bridgewater, New Jersey 08807-2862
Telephone No. 908-203-6504
Facsimile No. 908-203-6515